(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 December 2003 (04.12.2003)

PCT

(10) International Publication Number
WO 03/099198 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/IN03/00198

(22) International Filing Date: 26 May 2003 (26.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
464/MUM/2002 24 May 2002 (24.05.2002) IN

(71) Applicant *(for all designated States except US)*: **SUN PHARMACEUTICAL INDUSTRIES LIMITED** [IN/IN]; ACME PLAZA, ANDHERI KURLA ROAD, ANDHERI EAST, 400059 MUMBAI (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PERIYANDI, Nagarajan** [IN/IN]; SUN PHARMA ADVANCED RESEARCH CENTRE, SPARC, AKOTA ROAD, AKOTA, 390020 BARODA (IN). **KILARU, Srinivasu** [IN/IN]; SUN PHARMA ADVANCED RESEARCH CENTRE, SPARC, AKOTA ROAD, AKOTA, 390020 BARODA (IN). **THENNATI, Rajamannar** [IN/IN]; SUN PHARMA ADVANCED RESEARCH CENTER, SPARC, AKOTA ROAD, AKOTA, 390020 BARODA (IN).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

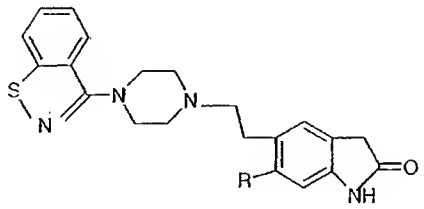
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

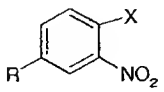
as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

[Continued on next page]

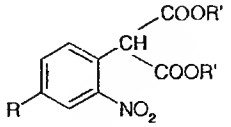
(54) Title: A PROCESS FOR THE PREPARATION OF OXINDOLE DERIVATIVES



(I)



(II)



(III)

(57) Abstract: A process for the preparation of oxindole derivative of formula (I) comprising reacting compound of formula (II) with dialkyl malonate, COOR1-COOR1, in the presence of a mild base to give compound of formula (III); and wherein R is selected from hydrogen, linear, branched or cyclic alkyl, aryl, substituted aryl, heteroaryl, haloalkyl like CF_3, alkoxy, haloalkoxy, thioalkyl and halogen.; R^1 is selected from linear, branched and cyclic alkyl (C_1 to C_4 groups); and X is selected from chloro, bromo, fluoro and iodo groups;further converting compound of formula (III) to compound of formula (I).

WO 03/099198 A2

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

— *of inventorship (Rule 4.17(iv)) for US only*

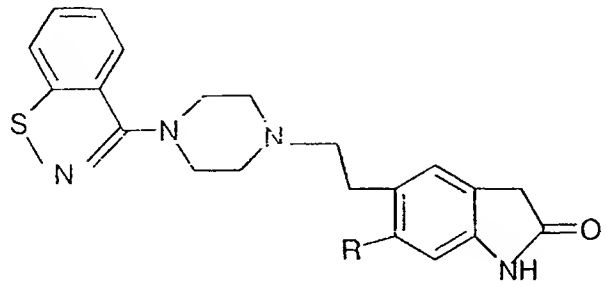
Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A PROCESS FOR THE PREPARATION OF OXINDOLE DERIVATIVES

The present invention relates to a process for the preparation of oxindole derivative of formula I.



formula I

wherein R is selected from hydrogen, linear, branched or cyclic alkyl, aryl, substituted aryl, heteroaryl, haloalkyl like CF_3, alkoxy, haloalkoxy, thioalkyl and halogen.

The compound of formula I, wherein R is chloro i.e. 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one oxindole is commonly known as ziprasidone (INN name) which is used in the treatment of schizophrenia.

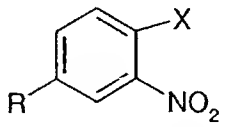
PRIOR ART

United States Patent No. 4831031 (hereinafter described as **'031**) discloses the preparation of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one, compound of formula I, by reacting 6-chloro-oxindole with chloroacetyl chloride followed by reducing the carbonyl group with trifluoroacetic acid/triethylsilane to yield 5-(2-chloroethyl)-6-chlorooxindole. 5-(2-chloroethyl)-6-chlorooxindole is then reacted with 3-(1-piperazinyl)-1,2-benzisothiazole to give compound of formula I, ziprasidone.

United States Patent No. 5338846 (hereinafter described as **'846**) discloses preparation of compound of formula I, wherein R is chloro, by reacting 5-(2-

chloroethyl)-6-chlorooxindole with 3-(1-piperazinyl)-1,2-benzisothiazole followed by preparation of mono hydrate of its hydrochloride salt.

Both the above patents do not disclose the preparation of compound of formula I from 2,5-dichloronitrobenzene, compound of formula II. Further, **'031** discloses reaction of 6-chloro oxindole with chloroacetyl chloride in carbon disulfide solvent which is difficult to handle at commercial scale because of its inherent properties viz. highly volatile, inflammable and hazardous.



formula II (wherein R and X are chloro)

In literature, several procedures for the synthesis of oxindole derivatives are reported. G.J.Quallich reported a process (**Synthesis, 51, January 1993**) involving the reaction of a substituted halo nitrobenzene with a malonate, usually dimethyl malonate, in the presence of sodium hydride, to obtain the diester of arylmalonate. The second step involves Krapcho decarboxylation of the diester of the arylmalonate with lithium chloride in dimethyl sulfoxide to obtain the malonate monoester. The nitro group of the monoester is then reduced with iron and acetic acid to yield the substituted oxindole derivative. The disadvantage of this method is the use of sodium hydride in the preparation of the diester of the arylmalonate. Sodium hydride is a highly moisture sensitive and pyrophoric compound, thereby making its use on an industrial scale highly hazardous. Further, the overall yield reported by this process is about 50%.

United States Patent No. 4,160,032 discloses the preparation of 6-chloro-oxindole, wherein 4-chloro-2-nitrotoluene is treated with sodium ethoxide and diethyl oxalate, followed by refluxing it with hydrogen peroxide and acidification, to obtain 4-chloro-2-nitrophenylacetic acid. The 4-chloro-2-nitrophenylacetic acid is then subjected to

reductive cyclisation using hydrogen gas under pressure, in the presence of PtO_2, to obtain 6-chloro-oxindole. This patent discloses a route starting with 4-chloro-2-nitrotoluene and not 2,5-dichloronitrobenzene, compound of formula II, as prepared in the process of the present invention. Further, it reduces the nitro group in the presence of PtO_2 catalyst which could probably give dehalogenated products.

Collins et al reported a process (**J. Am. Chem. Soc., 221, 78, 1956**) wherein nitrophenylacetic acids were prepared from o-nitrotoluenes through pyruvic acids. These nitrophenylacetic acids were further subjected to reduction using zinc and sulfuric acid to yield the oxindoles. The disadvantage of this process is that the nitrophenylacetic acids were obtained in moderate yields, and in the case of 4-chloro-2-nitrophenylacetic acid, a precursor of 6-chloro-oxindole, a yield as low as 4% was reported.

PCT pulication 02/14275 also discloses the synthesis of 6-halosubstituted oxindoles using 4-halo-2-nitrophenylacetic acid as the starting material. The starting material is subjected to reductive cyclisation using 50% sulfuric acid and zinc dust in the presence of ethanol as the solvent. The entire process is carried out at high temperature under a nitrogen blanket. Such a process is not feasible at industrial scale because the working up of the reaction involves extraction in organic solvents, followed by chromatographic separation of the final product.

Another process for the preparation of halosubstituted oxindoles is disclosed in Czechoslovakian Patent No. 191777, wherein a 3-halosubstituted aniline is reacted with chloroacetyl chloride, followed by refluxing the mixture with aluminum chloride in a suitable solvent to obtain the 6-halosubstituted oxindole. The disadvantage of this process is that it could also lead to formation of the regio isomer, viz. 4-chloro-oxindole, that needs to be separated from the final product.

Japanese Patent Nos. 56068668 and 62028133 disclose the process for the preparation of unsubstituted oxindole using 2-chlorophenylacetic acid as the starting material.

The 2-chlorophenylacetic acid is cyclised to the oxindole, using aqueous ammonia in the presence of CuCl. Such a procedure may not be feasible for dihalo compounds, wherein the dihalo compound could lead to the formation of a mixture of products, such as the undesired mono and/or diaminohalo compounds. Hence, the process is undesirable for the synthesis of substituted oxindoles.

OBJECT OF THE INVENTION:

The object of the present invention is to provide a simple, cost-effective and non-hazardous process for the preparation of compound of formula I.

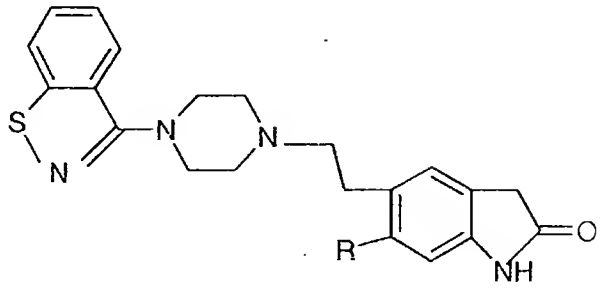
A more specific object is to prepare compound of formula I, wherein R is chloro, using a simple, cost-effective and non-hazardous process.

Another object of the present invention is to prepare compound of formula V which is an intermediate for the preparation of compound of formula I.

The present invention provides a process for the preparation of compound of formula I involving synthesis of the diester of arylmalonate from 2,5-dichloronitrobenzene, compound of formula II, wherein a mild, readily available, cheap and non-hazardous base is used, as opposed to prior art use of reactive bases such as sodium hydride. The advantage of using a mild base such as an alkali carbonate or an alkaline earth metal carbonate is that it does not necessitate the use of absolutely anhydrous reaction conditions. The prior art also reports the use of two equivalents of dialkyl malonate in the synthesis of the diester of the arylmalonate, in order to suppress the formation of the dialkyl bisarylmalonate impurity. We have surprisingly found that the use of mild and readily available bases along with 0.5 to 1.5 moles of the dialkyl malonate results in the formation of a pure product of formula III (greater than 99%) in high yield which is then further converted to compound of formula I.

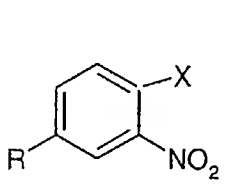
SUMMARY OF INVENTION :

A process for the preparation of compound of formula I the process comprising

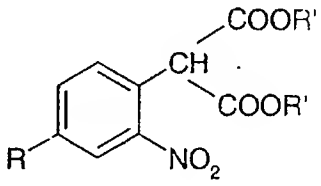


formula I

reacting compound of formula II with dialkyl malonate, $COOR^1$-$COOR^1$, in the presence of a mild base to give compound of formula III; and



formula II



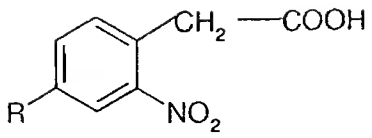
formula III

wherein R is selected from hydrogen, linear, branched or cyclic alkyl, aryl, substituted aryl, heteroaryl, haloalkyl like CF_3, alkoxy, haloalkoxy, thioalkyl and halogen.; R^1 is selected from linear, branched and cyclic alkyl (C_1 to C_4 groups); and X is selected from chloro, bromo, fluoro and iodo groups;

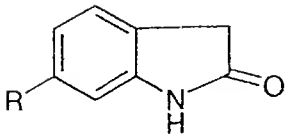
further converting compound of formula III to compound of formula I.

More particularly, compound of formula III is converted to compound of formula I by process comprising

(a) hydrolyzing and decarboxylating compound of formula III to give compound of formula IV;



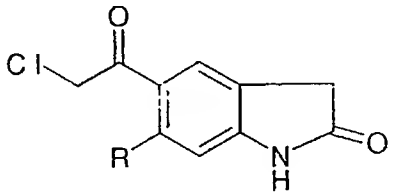
formula IV



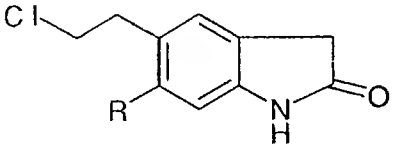
formula V

(b) reducing and cyclizing compound of formula IV to yield compound of formula V;

(c) reacting compound of formula V with chloroacetyl chloride to yield compound of formula VI;



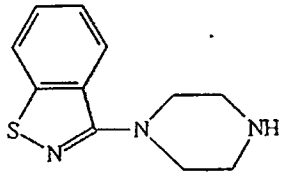
formula VI



formula VII

(d) reducing compound of formula VI to compound of formula VII: and

(e) reacting compound of formula VII with compound of formula VIII to yield compound of formula I or its pharmaceutically acceptable salts.

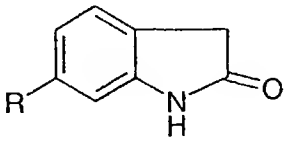


formula VIII

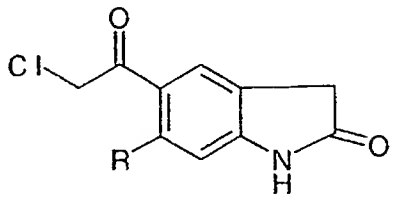
DETAILED DESCRIPTION OF THE INVENTION:

Accordingly, the process of the present invention provides a process for the preparation of oxindole derivative of formula I, wherein a substituted or unsubstituted halonitrobenzene (II) is used as the starting material. Compound of formula II is reacted with a dialkyl malonate in the presence of an alkali carbonate or an alkaline earth metal carbonate to obtain the corresponding diester of the arylmalonate (III).

This diester of the arylmalonate (III) is then converted to the corresponding arylacetic acid derivative (IV), followed by reduction and cyclization of the acid derivative formed to yield the substituted or unsubstituted oxindole, compound of formula V.



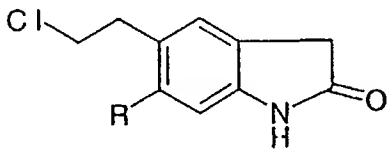
formula V



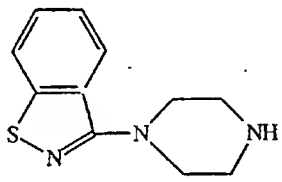
formula VI

Compound of formula V is then converted to compound of formula VI by reacting with chloroacetylchloride. Compound of formula VI is converted to compound of formula I by known processes. Method of preparing compound of formula I from compound of formula VI is disclosed in **United States Patent No. 4831031.**

Preferably, the process of the present invention prepares compound of formula I from compound of formula V by reacting with chloroacetyl chloride in an organic solvent selected from halo or nitro substituted alkanes and benzene, to give compound of formula VI, followed by reduction of compound of formula VI to yield compound of formula VII and reacting compound of formula VII with compound of formula VIII.



Formula VII



formula VIII

According to the process of the present invention compound of formula I is prepared by reacting substituted or unsubstituted halonitrobenzene with a dialkyl malonate to form diester of the arylmalonate.

In a preferred embodiment of the present invention, the substituted or unsubstituted halonitrobenzene is reacted with 0.5 to 1.5 moles of a dialkyl malonate, preferably 1

to 1.5 moles of a dialkyl malonate, more preferably with 1 to 1.2 moles of a dialkyl malonate. The reaction is carried out in the presence of a mild base selected from the group comprising alkali carbonates, alkaline earth metal carbonates and oxides. In preferred embodiments an alkali carbonate is used as the base, more preferably the alkali carbonate is potassium carbonate. The reaction of the halonitrobenzene with the dialkyl malonate is carried out using a polar protic solvent, polar aprotic solvent, aromatic high boiling solvent or aliphatic high boiling solvent, having a boiling point above 70^0C. In preferred embodiments, the solvent used is a polar aprotic solvent, more preferably the solvent used is dimethyl sulfoxide (DMSO). The reaction is carried out at a temperature ranging from about 50^0C to about 130^0C, preferably from about 70^0C to about 120^0C, more preferably from about 80^0C to about 100^0C.

According to the process of the present invention step (a) involves conversion of the diester of arylmalonate to the corresponding aryiacetic acid derivative. In a preferred embodiment, step (a) is carried out in the presence of mineral acid. The diester of the arylmalonate is treated with a mineral acid. The mineral acid may be selected from hydrochloric acid, sulfuric acid and nitric acid, the most preferred being hydrochloric acid. For instance, the volume of concentrated hydrochloric used in the reaction ranges from about 3 to 7 parts by weight of compound of formula III. The conversion may be carried out in the presence or absence of an organic acid such as acetic acid. When an organic acid is used the ratio of mineral acid to organic acid ranges from about 10:1 to about 1:1, preferably from about 10:2 to about 10:6, more preferably from about 10:3 to about 10:5. The reaction is carried out in the absence of lithium salt.

The reaction is carried out at a temperature ranging from about 40^0C to about 120^0C, preferably from about 60^0C to about 110^0C, more preferably from about 90^0C to about 110^0C.

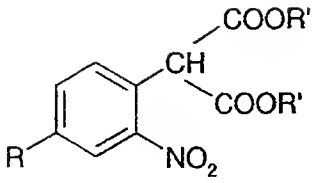
According to the process of the present invention step (b) involves reduction and cyclization of the arylacetic acid derivative to form the substituted or unsubstituted

oxindole. In a preferred embodiment, the arylacetic acid derivative is reduced using iron-acetic acid, in the presence or absence of a co-solvent. The co-solvent, if used, may be selected from a group comprising linear, branched or cyclic alcohols having C_1-C_{10} atoms. In preferred embodiments the co-solvent used is a C_1 to C_5 alcohol, more preferably a C_1 to C_3 alcohol. The co-solvent is used in an amount ranging from about 1% to about 50% by volume of the reaction mixture, preferably from about 20% to about 50% by volume of the reaction mixture, more preferably from about 15% to about 30% by volume of the reaction mixture.

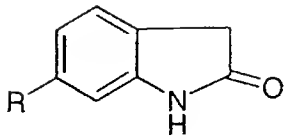
In a preferred embodiment, the oxindole derivative obtained by the process of the present invention is 6-chloro-oxindole, also known as 6-chloro-indol-2-one. In a preferred embodiment, the process for preparation of the 6-chloro-oxindole involves conversion of 2,5-dichloronitrobenzene to the corresponding dimethyl ester of malonate using dimethyl malonate in the presence of potassium carbonate and dimethyl sulfoxide. The dimethyl ester of malonate is then reacted with 10N hydrochloric acid in the presence of acetic acid to yield the corresponding arylacetic acid. This acid is then reduced and cyclized using standard reaction conditions such as iron and acetic acid, in the presence or absence of a co-solvent such as methanol to yield 6-chloro-oxindole.

According to the present invention step (c) comprises reaction of compound of formula V with chloroacetyl chloride in an organic solvent selected from halo or nitro substituted alkanes or benzene such as methylene dichloride, nitromethane, nitrobenzene, chloroform, carbon tetrachloride and the like, preferably methylene dichloride

In a preferred embodiment of the process of the present invention the first step for the preparation of compound of formula I is carried out in the presence of a mild base to yield compound of formula III followed by hydrolysis, decarboxylation, reduction and cyclization to yield compound of formula V,

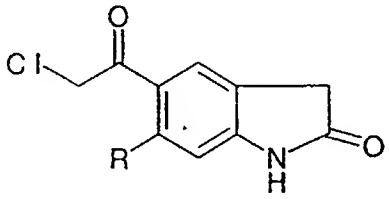


formula III

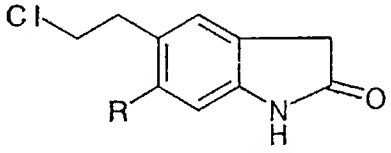


formula V

reacting compound of formula V with chloroacetyl chloride in an organic solvent selected from halo or nitro substituted alkanes or benzene such as methylene dichloride, nitromethane, nitrobenzene, chloroform, carbon tetrachloride and the like to yield compound of formula VI and converting compound of formula VI to compound of formula I by the steps

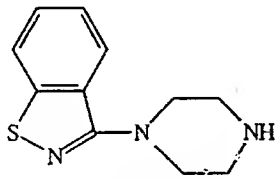


formula VI



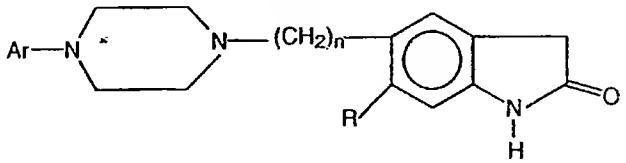
formula VII

- reducing compound of formula VI to compound of formula VII and
- reacting compound of formula VII with compound of formula VIII to give compound of formula I.



formula VIII

The oxindole derivatives, compound of formula V and VI, synthesized by the process steps of the present invention can be used as intermediates for the syntnesis of pharmaceutically active antipsychotic compounds and other therapeutically active compounds bearing the following general structure –



where Ar is benzoisothiazolyl or an oxide or dioxide thereof each optionally substituted by one fluoro, chloro, trifluoromethyl, methoxy, cyano, or nitro; n is 1 to 5, and R is hydrogen or halogen, or as described earlier.

5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H-indol-2-one, compound of formula I or ziprasidone is prepared from compound of formula VI by any known prior art such as United States Patent No. 4831031 or United States Patent No. 5338846 The free base may be converted to its salt or hydrate form by using processes as disclosed in United States Patent No. 5312925.

The following examples do not limit the scope of the invention and are included as illustrations.

EXAMPLES

Example 1

Preparation of dimethyl-(4-chloro-2-nitrophenyl)malonate – Dimethyl malonate (189.2gm, 1.43 moles) is added to a mixture of anhydrous potassium carbonate (360gm, 2.6 moles) and dimethyl sulfoxide (3 liters) under a nitrogen atmosphere at 25-30^{0}C. The reaction mixture is heated to 60-65^{0}C and 2,5-dichloronitrobenzene (250gm, 1.3 moles) is added to it in portions over a period of one hour. The temperature of the reaction mixture is then raised to 80-85^{0}C, maintained so for 15 hours, and cooled to 40-45^{0}C. A mixture of water (2 liters) and concentrated hydrochloric acid (0.5 liters) is then used to quench the reaction mixture at 15-25^{0}C. Hexane (500ml) is then added to this and stirred for an hour at 20-25^{0}C. The dimethyl-(4-chloro-2-nitrophenyl)malonate formed is filtered and washed with water till the mother liquor shows a pH of 6.5-7. The product is finally washed with hexane and dried at 40-45^{0}C under vacuum.

Example 2

Preparation of 4-chloro-2-nitrophenylacetic acid – Dimethyl-(4-chloro-2-nitrophenyl)malonate (100gm) is mixed with acetic acid (200ml) at 20-25^{0}C, followed by slow addition of concentrated hydrochloric acid (500ml). The reaction mixture is heated to 95-100^{0}C, maintained at this temperature for 6 hours and cooled to 5-10^{0}C. Chilled water (1000ml) is then added to the reaction mixture and stirred for 30 minutes. The solid 4-chloro-2-nitrophenylacetic acid thus obtained is filtered and washed with water till the mother liquor shows a pH of 6.5-7. The product is dried at 65-70^{0}C under vacuum.

Example 3

Preparation of 6-chloro-oxindole – 4-chloro-2-nitrophenylacetic acid (100gm) is mixed with acetic acid (250ml) and methanol (250ml) at 25-30^{0}C. The reaction mixture is then heated to 50-55^{0}C and iron powder (64.7 gm) is then added to it. The temperature is raised to about 75^{0}C and the reaction mixture is heated with stirring for an hour. The reaction mixture is then cooled to 40-45^{0}C and chilled water (5 liters) is added to it, followed by concentrated hydrochloric acid (0.5 liters). The temperature is maintained at 20-25^{0}C. The 6-chloro-oxindole thus obtained is filtered, washed

with water till the mother liquor shows a pH of 4.5-5.5, and dried at 70^{0}C under vacuum.

Example 4

Preparation of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one :

(i) Preparation of 6-chloro-5-(chloroacetyl)oxindole : Charge 250 ml of methylene dichloride and 100 gm of 6-chloro-oxindole in a 3 litre three neck flask under nitrogen atmosphere at 25 to 30^{0}C. Cool gradually to 0 to 5^{0}C under stirring and charge 199 gm of anhydrous aluminium chloride in portions at 0 to 5^{0}C and stir for 15 min at 0 to 5^{0}C. Add 87.6 gm of chloroacetyl chloride slowly at 0 to 5^{0}C over 30 mins. Stir at 0 to 5^{0}C for 30 mins. Heat the reaction mixture slowly to reflux (40 to 45^{0}C) over 30 mins. Reflux for 12 hrs. On completion of reaction cool the reaction mixture to 25 to 30^{0}C, pour into 1 kg ice, 50 ml of conc. HCl and 450 ml of demin water at 0 to 10^{0}C under stirring over 30 mins. Stir for 30 mins, filter solid product and wash with demin water. Prepare a slurry of the solids in hexane and suck dry the product. Dry the product at 70 to 75^{0}C.

(ii) Preparation of 5-(2-chloroethyl)-6-chlorooxindole: Charge 650 ml of trifluoroacetic acid and 130 gm of step (i) product into a 3 litre three neck flask under nitrogen atmosphere at 25 to 30^{0}C. Stir the mixture for 15 mins and cool to 0 to 5^{0}C under stirring. Charge 142.46 gms of triethylsilane slowly keeping temperature between 0 to 5^{0}C over 30 mins. Stir the reaction mixture for 30 mins at 0 to 5^{0}C and allow it to gradually reach 30 to 35^{0}C. Stir the reaction for 6 hrs. Cool the reaction mixture to 5 to 10^{0}C and add chilled water slowly. Stir the mixture for 1 hr and filter the solids. Wash with demin water, 5% $NaHCO_3$, demin water and hexane. Suck dry product and dry at 70 to 75^{0}C.

(iii) Preparation of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one :

Charge 1.0 litre demin water, 100 gm of step (ii) product, 122.4 gm 3-(1-piperazinyl)-1,2-benzisothiazole HCl and 138.2 gm of sodium carbonate into a 3 litre three neck flask at 25 to 30^{0}C. Stir for 15 mins and heat to reflux temperature 95 to 100^{0}C. Maintain at reflux temperature for 15 hrs.

Cool the reaction mixture to 45 - 50^{0}C. Add 1.0 lt of demin water into the reaction mixture and stir for 30 mins. Filter at 45 to 50^{0}C and wash with demin water. Suck dry for 30 mins to yield crude product. Charge 2 lt of demin water and above crude product and heat the mixture gradually to 45 to 50^{0}C and stir for 30 mins. Filter the product at 45 to 50^{0}C and wash with demin water. Suck dry the product for 30 mins. Charge 2.0 lt of demin water and 300 gm of crude product into a 1.0 litre three neck flask at 25 to 30^{0}C and heat the mixture gradually to 45 to 50^{0}C. Stir for 30 mins. Filter the product at 45 to 50^{0}C and wash with demin water till about neutral pH (6.5 to 7.0). Suck dry the product for 30 mins to get wet crude base 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one.

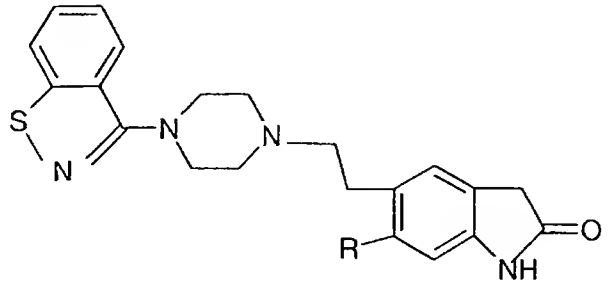
Add 300 gms of wet crude base and 1.0 lt of isopropanol at 25 to 30^{0}C. Warm the reaction mixture to 50 to 55^{0}C and stir for 1.0 hr. Cool the reaction mixture gradually to 10 to 15^{0}C and stir for 30 mins. Filter the product and wash with chilled isopropanol. Suck dry for 30 mins. Charge 300 gm of wet crude base and 6 lt of tetrahydrofuran (THF). Heat the reaction mixture gradually to reflux temperature 65-70^{0}C. Reflux till clear solution. Cool to 50 to 55^{0}C and add charcoal and stir for 30 min at 50 to 55^{0}C. Filter the charcoal and wash with hot THF. Distill out THF at 50 to 55^{0}C under vacuum till residual volume is 1 lt and cool the reaction mixture gradually to 5 to 10^{0}C and stir for 1 hr. Filter the product and wash with chilled THF. Suck dry the product for 30 mins. Dry the product at 60 to 65^{0}C.

(iv) Preparation of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one hydrochloride:

Charge 1.56 lt of demin water, 173 ml of conc hydrochloric acid in a 3 lt three neck flask and stir for 15 mins at 25 to 30^{0}C. Charge 115 gm of 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-di hydro-2H- indol-2-one free base to the above HCl solution and stir for 15 mins. Heat the reaction mixture gradually to 65 to 70^{0}C and stir for 24 hrs. Cool the reaction mixture to 25 to 30^{0}C and stir for 30 mins. Charge 230 ml of 1N HCl solution to the reaction mixture and stir for 3 hrs. Filter the product and wash with 1150 ml of demin water till pH of mother liquor becomes 5 to 7.5. Suck dry the product for 30 mins. Dry the product at 50 to 55^{0}C.

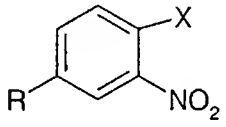
We Claim:

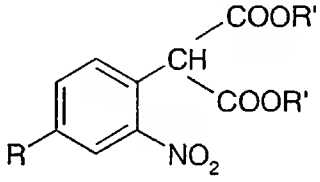
1. A process for the preparation of oxindole derivative of formula I comprising



formula I

reacting compound of formula II with dialkyl malonate, $COOR^1$-$COOR^1$, in the presence of a mild base to give compound of formula III; and





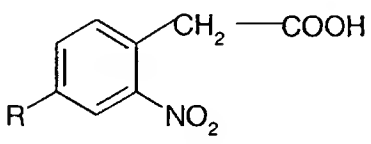
formula II formula III

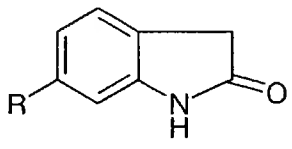
wherein R is selected from hydrogen, linear, branched or cyclic alkyl, aryl, substituted aryl, heteroaryl, haloalkyl like CF_3, alkoxy, haloalkoxy, thioalkyl and halogen.; R^1 is selected from linear, branched and cyclic alkyl (C_1 to C_4 groups); and X is selected from chloro, bromo, fluoro and iodo groups;

further converting compound of formula III to compound of formula I.

2. A process as claimed in claim 1 wherein the process for converting compound of formula III to compound of formula I comprises

(a) hydrolyzing and decarboxylating compound of formula III to give compound of formula IV;

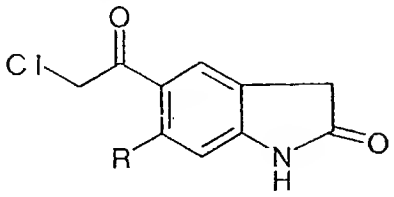




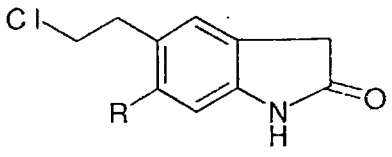
formula IV formula V

(b) reducing and cyclizing compound of formula IV to yield compound of formula V;

(c) reacting compound of formula V with chloroacetyl chloride to yield compound of formula VI;



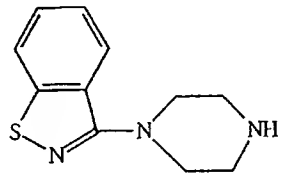
formula VI



formula VII

(d) reducing compound of formula VI to compound of formula VII: and

(e) reacting compound of formula VII with compound of formula VIII to yield compound of formula I or its pharmaceutically acceptable salts.



formula VIII

3. A process as claimed in claim 2 wherein R is chloro.
4. A process as claimed in claim 2 wherein the mild base is selected from alkali, alkaline earth metal carbonates and oxides.
5. A process as claimed in claim 2 step (a) wherein hydrolysis and decarboxylation is carried out in the presence of mineral acid.
6. A process as claimed in claim 1 wherein step (b) is carried out with iron-acetic acid in the presence or absence of co-solvent.
7. A process as claimed in claim 1 wherein step (c) is carried out in an organic solvent selected from halo or nitro substituted alkanes (C_1 to C_4) and benzene.